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Commentary

Autophagy in preeclampsia: A new target?

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Preeclampsia is a multi-system disorder of pregnancy that affects 5–8% of pregnancies world-wide [1, 2]. Preeclampsia is characterized by new-onset hypertension with other organ dysfunction such as in the kidneys or liver, or neurological disturbances, occurring after the 20th week of gestation [3]. The underlying mechanisms of preeclampsia have yet to be fully elucidated. While the exact mechanism that leads to preeclampsia is still unknown, it is widely accepted that inadequate invasion of the uterine spiral arteries by cytotrophoblast cells during early pregnancy is one of the initiating events [2]. This shallow invasion of the cytotrophoblast cells leads to poor placentation and vascularization (i.e. ischemic placenta) in early pregnancy, eventually leading to systemic maternal endothelial dysfunction and immune cell activation, all thought to be the inciting processes leading to the clinical manifestations of preeclampsia [2]. Yet the molecular mechanisms that mediate this dysfunction remain under investigation.

During normal pregnancies, placental autophagy (an intracellular system for bulk degradation of damaged or dysfunctional cellular components) is critical for maintenance of cellular homeostasis that is needed for embryo development [4]. Autophagy is activated in response to environmental stress, however dysregulation of autophagy is associated with various diseases [5]. For example, impaired autophagy is associated with aging, neurodegenerative diseases, lysosomal disorders and cancer. In cancer, dual roles for autophagy have been described. During tumor initiation and malignant transformation, autophagy is considered to be tumor suppressive by inhibiting proliferation of cells. However, during the period of increased tumor growth, autophagy is thought to be beneficial by providing the cellular metabolites and glucose needed for proliferation and maintaining homeostasis of the tumor cells [5,6].

Studies of autophagy in preeclampsia provide conflicting roles of this homeostatic mechanism on preeclampsia development and progression [7]. In this issue of *EBioMedicine*, Zhao and colleagues report the results of a hybrid study using clinical placental samples and a mouse model of preeclampsia to identify a novel preeclampsia-associated regulator of autophagy [8]. The regulation of autophagy in preeclampsia is an area of research that has been increasing in interest over the past several years and the results reported in this featured article sought to identify a new target with therapeutic potential. Analysis of mRNA levels and protein expression of protein kinase C isoform β (PKCβ) in control and preeclamptic patient placentas demonstrated significantly lower expression of PKCβ in preeclampsia [8]. Furthermore, analysis of PKCβ mRNA expression using the Gene Expression Omnibus (GEO) dataset confirmed suppression of PKCβ in preeclampsia. Blockade of PKCβ in pregnant mice led to the activation of autophagy and the development of a preeclampsia-like phenotype, as evidenced by hypertension, proteinuria, and fetal growth restriction. Furthermore, inhibition of autophagy reduced blood pressure and proteinuria in the preeclampsic model. It was demonstrated that PKCβ inhibition was associated with angiogenic imbalance, but not inadequate trophoblast invasion. Understanding the mechanisms leading to the development of preeclampsia is critical to the development of effective treatment strategies for this maternal syndrome.

The findings from the study by Zhao et al. have provided additional insight into the potentially complex network between the PKC pathway and now autophagy [8]. Importantly, activation of autophagy is thought to be associated with immune activation, which is increased in the setting of preeclampsia, with a role in facilitating antigen presentation on MHCII [5,7]. Immune activation and autophagy are also linked to dysregulation of the Fas Ligand pathway which has been implicated in contributing to inadequate trophoblast invasion during preeclampsia [9,10]. The findings from Zhao et al. emphasize the need to understand the role of autophagy in trophoblast remodeling. Additionally, given the relationship between PKCβ inhibition and antiangiogenic imbalance apart from trophoblast invasion, more studies are warranted to understand the timescale for dysregulation of this pathway may occur in pregnancy.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Authors' contributions

DCC wrote the initial draft of the manuscript. DCC and KW edited and approved the final draft of the manuscript.

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